

Diastereoselective Allylation of 3,4-Dihydro-4-phenylisoquinoline. Convenient Methods for the Preparation of *cis*- and *trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline[#]

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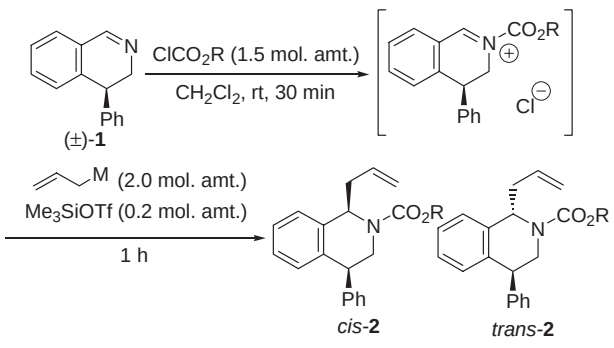
Diastereoselective allylation of 3,4-dihydro-4-phenylisoquinoline by several allylating reagents was examined. Reactions using allyltin or allylsilane in the presence of alkyl chloroformate and a catalytic amount of trimethylsilyl triflate gave *trans*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline with moderate diastereoselectivity. In contrast, *cis*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was obtained predominantly in the reactions using allyllithium, triallylborane, allylzinc bromide, and diallylzinc. *cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was transformed to (6*S**,10b*R**)-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline, a potential antidepressant agent, in five steps.

Diastereoselective allylation of imines or imine derivatives provides functionalized amines, which are useful intermediates in the synthesis of biologically active compounds and pharmaceutical substances.[1,2] 3,4-Dihydroisoquinoline derivatives, including imine *N*-oxides and iminium ions, have been employed as suitable precursors for preparations of various isoquinoline alkaloids and their analogues.[3] Although allylation of 3-substituted 3,4-dihydroisoquinolines has been reported,[4] there has been no report on the diastereoselective allylation of 4-substituted 3,4-dihydroisoquinolines to the best of our knowledge. Thus, we started an investigation of diastereoselective allylation of 3,4-dihydro-4-phenylisoquinoline (**1**) using various allylating reagents, because the allyl group can be later transformed conveniently to various functional groups, for example, alcohol via hydroboration, carbonyl group via oxidative cleavage, etc. After examination of allylating reagents and reaction conditions, we found complementary methods for the preparation of *trans*- and *cis*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline. (6*S**,10b*R**)-Hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline, a potential antidepressant agent, was obtained from *cis*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline in five steps.

Results and Discussion

First, diastereoselective allylation of 3,4-dihydro-4-phenylisoquinoline (**1**) was examined using allyltin or allylsilane in the presence of imino group activator as high *trans*-selectivity has been reported in the reaction of 3-substituted 3,4-dihydroisoquinoline derivatives in a similar manner.[4] Namely, isobutyl chloroformate (1.5 molar amount) was added to a CH_2Cl_2 solution of **1** at room temperature, and the solution was stirred at the temperature for 30 min. Then, allyltributyltin (2.0 molar amount) was added to the solution. After 24 h, allyl adduct **2a** was obtained in 57% yield as a mixture of diastereomers. The diastereomers were separated by preparative thin-layer chromatography, and the ratio of *cis*-**2a** and *trans*-**2a** was 30:70 (Table 1, Entry 1). Then, trimethylsilyl triflate (0.2 molar amount) was added together with allyltributyltin to improve the yield, because trimethylsilyl triflate is known to promote the reaction.[5] The reaction was completed in 1 h, and the yield was 70%, but the diastereoselectivity decreased (*cis*-**2a**:*trans*-**2a** = 33:67) (Table 1, Entry 2). When the reaction was carried out using allyltriphenyltin in place of allyltributyltin, both the yield and the diastereoselectivity improved (90% yield, *cis*-**2a**:*trans*-**2a** = 29:71) (Table 1, Entry 3). Next, a reaction using allylsilane, a less toxic reagent than allyltin, was carried out under the same reaction conditions in the presence of trimethylsilyl triflate, and the diastereoselectivity improved slightly (*cis*-**2a**:*trans*-**2a** = 27:73) (Table 1, Entry 4). When

Table 1. Allylation of **1** Using Allyltin or Allylsilane



	R	M	**2**	Yield/%	*cis*-**2**:*trans*-**2**
1[a)]	*i*-Bu	$SnBu_3$	**a**	57	30:70
2	*i*-Bu	$SnBu_3$	**a**	70	33:67
3	*i*-Bu	$SnPh_3$	**a**	90	29:71
4	*i*-Bu	$SiMe_3$	**a**	87	27:73
5	Bn	$SiMe_3$	**b**	80	32:68
6	Et	$SiMe_3$	**c**	85	31:69

a) Reaction was carried out for 24 h without using trimethylsilyl triflate.

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the reaction was carried out using benzyl chloroformate or ethyl chloroformate in place of isobutyl chloroformate, the diastereomer ratios were *cis*-**2b**:*trans*-**2b** = 32:68 and *cis*-**2c**:*trans*-**2c** = 31:69, respectively (Table 1, Entries 5 and 6). The stereochemistry of the products was assigned by comparing with authentic samples, prepared from *cis*- or *trans*-**3** and the corresponding alkyl chloroformate, and the stereochemistry of *trans*-**3** was determined based on the X-ray crystallographic analysis of *trans*-**4** (vide infra).

The stereochemical course of the reaction is explained by assuming a non-chelating open-chain transition state, depicted in Fig. 1. Allyltin or allylsilane approaches from less hindered side of the iminium intermediate to form *trans*-**2** predominantly.

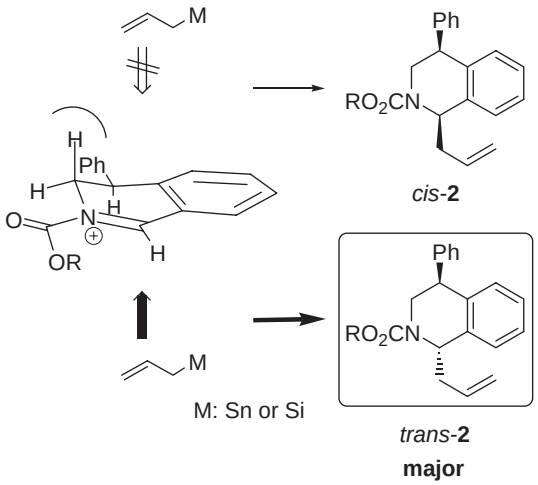


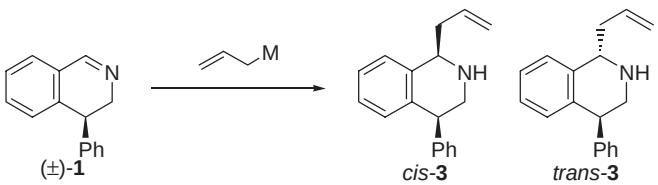
Fig. 1. Proposed stereochemical course of the allylation of **1** with allyltin or allylsilane in the presence of alkyl chloroformate.

Next, allylation of **1** using an allylmetallic reagent, which can interact with nitrogen atom of the imine **1** and may enable the formation of a cyclic transition state, was examined to improve the stereoselectivity. At first, a Grignard reagent was employed. Allylmagnesium bromide, prepared from freshly distilled allyl bromide and magnesium turnings in THF at −5 °C, was added to a THF solution of **1** at −78 °C, and the reaction mixture was stirred at that temperature for 1 h. 1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**) was obtained in 86% yield; however, the diastereoselectivity was low (*cis*-**3**:*trans*-**3** = 44:56) (Table 2, Entry 1). The stereochemistry of the products was determined as follows: After separation of the diastereomers by preparative thin-layer chromatography, the less polar isomer was treated with di-*tert*-butyl dicarbonate and NaOH in dioxane–water to give a crystalline compound, which was determined to be *tert*-butyl *trans*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*trans*-**4**) by X-ray crystallographic analysis (Fig. 2).

Then, other allylmetallic reagents, such as allyllithium,[6] triallylborane,[7] and allylzinc bromide,[8] were examined to determine their effects on the diastereoselectivity of the reaction (Table 2, Entries 2–4). Interestingly, all these reagents gave *cis*-**3** predominantly, and the best result (82% yield, *cis*-**3**:*trans*-**3** = 84:16) was obtained when allylzinc bromide was employed (Table 2, Entry 4). Although the diastereoselectivity was improved slightly using diallylzinc,[9] the yield was lower (Table 2, Entry 5). The reaction of allylzinc bromide in Et_2O, cyclopentyl methyl ether (CPME), dimethoxymethane, or toluene did not improve the diastereoselectivity (Table 2, Entries 6–9).

We assume that the diastereoselectivity of the reaction of **1** and allyllithium, triallylborane, and allylzinc reagent is due to the following: Two six-membered chair-like cyclic transition states, TS-A and TS-B, are possible by the coordination of

Table 2. Diastereoselective Allylation of **1** Using Allylmetallic Reagents



	Reagent	Solvent	Condition	Yield/%	*cis*-**3**:*trans*-**3**
1	allylmagnesium bromide (2.5 mol amt.)	THF	−78 °C, 1 h	86	44:56
2	allyllithium (2.5 mol amt.)	THF	−78 °C, 1 h	79	67:33
3	triallylborane (1.1 mol amt.)	THF	−78 °C, 1 h	82	65:35
4	allylzinc bromide (1.5 mol amt.)	THF	−78 °C, 2 h then rt, 1 h	82	84:16
5	diallylzinc (3.0 mol amt.)	THF	−78 °C, 2 h then rt, 1 h	76	86:14
6	allylzinc bromide (3.0 mol amt.)	Et_2O	−78 °C, 2 h then rt, 1 h	76	77:23
7	allylzinc bromide (3.0 mol amt.)	CPME	−78 °C, 2 h then rt, 1 h	86	80:20
8	allylzinc bromide (3.0 mol amt.)	dimethoxymethane	−78 °C, 2 h then rt, 1 h	79	77:23
9	allylzinc bromide (3.0 mol amt.)	toluene	−78 °C, 2 h then rt, 1 h	86	78:22

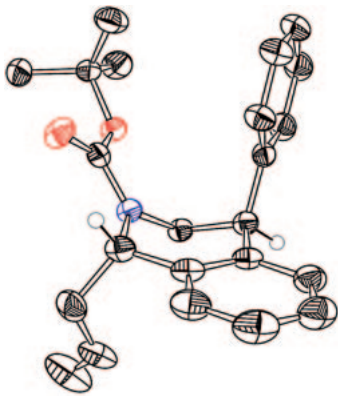


Fig. 2. ORTEP drawing of *trans*-**4** with thermal ellipsoids drawn at the 50% probability level. Some hydrogen atoms are omitted for clarity (Black = Carbon, Red = Oxygen, Blue = Nitrogen, and Gray = Hydrogen).

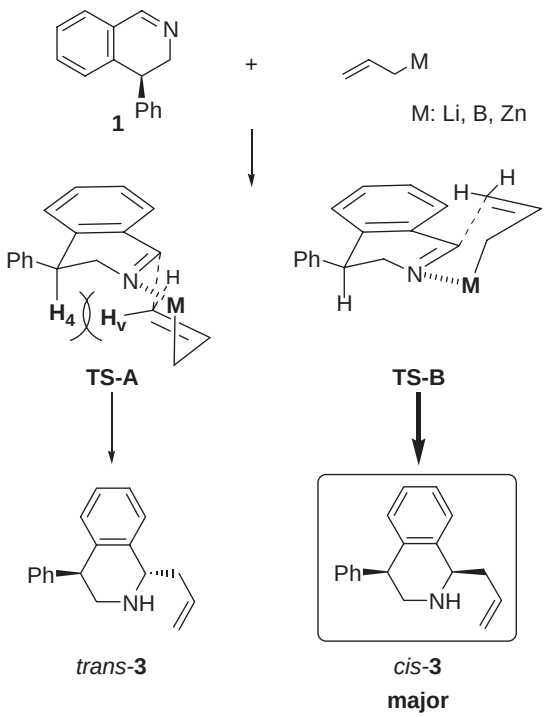
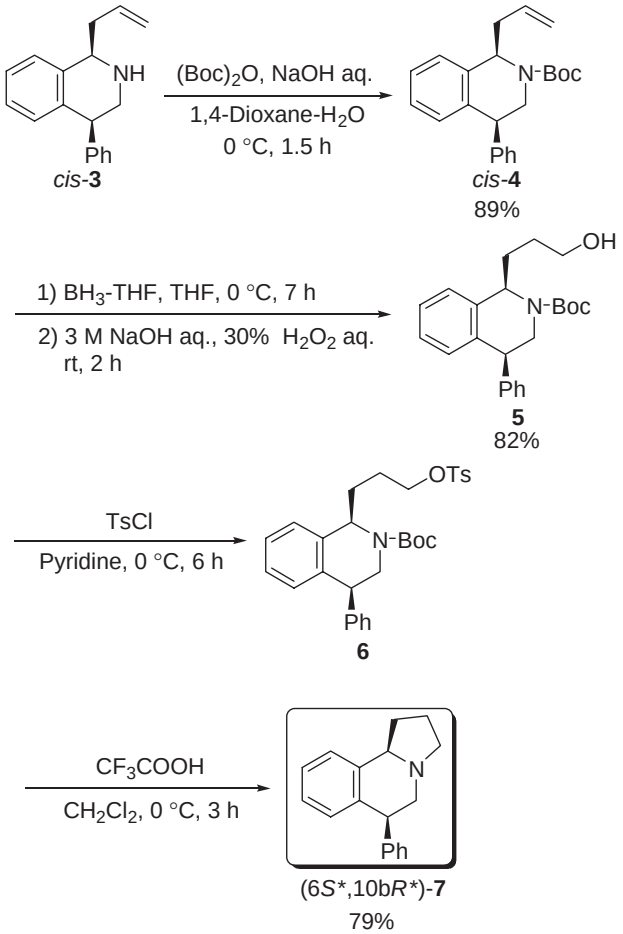


Fig. 3. Proposed transition states for the allylation of **1** with allylmetallic reagent (Li, B, and Zn).

the nitrogen atom of imine **1** to the allylmetallic reagent. Steric repulsion arises in TS-A between axial hydrogen (H_4) in C-4 position of dihydroisoquinoline ring and terminal vinylic hydrogen (H_v), whereas this repulsion is avoided in TS-B to give *cis*-**3** predominantly (Fig. 3).

As *cis*-**3** was obtained in good diastereoselectivity, the method was applied to the synthesis of (6*S**,10b*R**)-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline (**7**), which is a potential antidepressant agent.[10] Initially, the amino group in *cis*-**3** was protected using di-*tert*-butyl dicarbonate, and *tert*-butyl *cis*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*cis*-**4**) was obtained in 89% yield. Then, hydroboration of *cis*-**4** with BH_3–THF complex, followed by oxidation with NaOH–H_2O_2, gave the corresponding alcohol **5** in 82% yield.



Scheme 1. Synthesis of hexahydro-6-phenylpyrrolo[2,1-*a*]-isoquinoline (**7**).

The hydroxy group of **5** was converted to a leaving group by tosylation, and removal of *t*-butoxycarbonyl group of the tosylate **6** with trifluoroacetic acid afforded (6*S**,10b*R**)-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline (**7**) in 79% from **5** by spontaneous intramolecular cyclization (Scheme 1).

In summary, we developed a diastereoselective allylation reaction of 3,4-dihydro-4-phenylisoquinoline (**1**). Either *cis*- or *trans*-1-allyl-4-substituted 1,2,3,4-tetrahydroisoquinoline was obtained by choosing the appropriate allylating reagent. Namely, reaction using allylsilane in the presence of alkyl chloroformate and a catalytic amount of trimethylsilyl triflate gave *trans*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline with moderate diastereoselectivity, whereas *cis*-1-allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was obtained in good diastereoselectivity in the reaction using allylzinc bromide. The method was applied to the synthesis of (6*S**,10b*R**)-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline.

Experimental

General. Melting points were determined on a Stuart melting point apparatus SMP3 and are uncorrected. IR spectra were recorded on a HORIBA FT-730 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-EX-270 spectrometer. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Elemental analyses were carried out on a Vario EL III Elemental analyzer. Thin-layer chromatography analyses

were done on silica-gel 60 F_{254}-coated plates (E. Merck AG, Germany). Column chromatography was carried out with Wakogel C-200 gel and the indicated eluent. Preparative thin-layer chromatography was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm × 20 cm). Diethyl ether (Et_2O) (Dehydrated) and tetrahydrofuran (THF) (Dehydrated, stabilizer free), purchased from Kanto Chemical Co., Inc., were used in anhydrous reactions. Other solvents were purified according to standard procedures.

Addition Reaction of Allyltrimethylsilane to 3,4-Dihydro-4-phenylisoquinoline (1) in the Presence of Isobutyl Chloroformate and Trimethylsilyl Triflate (Table 1, Entry 4). Under an argon atmosphere, to a solution of 3,4-dihydro-4-phenylisoquinoline (**1**)[11] (60.9 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added isobutyl chloroformate (57 μL, 0.44 mmol) at room temperature. After stirring for 30 min, allyltrimethylsilane (94 μL, 0.59 mmol) and trimethylsilyl triflate (11 μL, 0.06 mmol) were added to the reaction mixture. Then, the reaction mixture was stirred for 1 h. CH_2Cl_2 and saturated aqueous $NaHCO_3$ were added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed successively with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was separated by preparative thin-layer chromatography (silica-gel, hexane/Et_2O = 10/1 ×3) to give *trans*-**2a** (67.9 mg, 64%) and *cis*-**2a** (24.7 mg, 23%).

Isobutyl *trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*trans*-2a): Colorless solid. mp: 65.4–65.6 °C (from hexane); IR (KBr, cm^{-1}): 3025, 2960, 1694, 1427, 1219, 1127, 914, 752, 699; ^{1}H NMR ($CDCl_3$): δ 0.58–0.91 (6H, m), 1.40–1.54 and 1.83–1.92 (1H, m), 2.64 (2H, t, J = 7.9 Hz), 3.38 (1H, dd, J = 6.6, 10.2 Hz), 3.55–3.81 (2H, m), 4.11–4.31 (2H, m), 5.01–5.09 (2H, m), 5.28–5.33 and 5.47–5.52 (1H, m), 5.82–5.98 (1H, m), 6.95 (3H, t, J = 9.7 Hz), 7.10–7.25 (6H, m); ^{13}C NMR ($CDCl_3$): δ 18.9, 19.0, 19.1, 27.7, 28.0, 41.1, 41.5, 44.5, 44.7, 53.6, 71.2, 71.4, 117.2, 117.5, 126.2, 126.5, 126.7, 128.1, 128.1, 129.9, 134.4, 134.7, 135.9, 136.9, 143.9, 155.7; Found: C, 78.99; H, 7.78; N, 3.82%. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01%.

Isobutyl *cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*cis*-2a): Colorless oil. IR (neat, cm^{-1}): 3027, 2960, 1699, 1427, 1219, 1126, 915, 758, 704; ^{1}H NMR ($CDCl_3$): δ 0.95 (6H, dd, J = 4.0, 6.6 Hz), 1.96 (1H, m), 2.71 (2H, t, J = 8.1 Hz), 3.15–3.33 (1H, m), 3.82–3.99 (2H, m), 4.11–4.23 (1H, m), 4.30 (dd, J = 5.9, 13.9 Hz) and 4.47 (dd, J = 6.3, 13.5 Hz) (1H), 5.06–5.13 (m, 2H), 5.28 (t, J = 7.0 Hz) and 5.43 (t, J = 7.0 Hz) (1H), 5.85–6.00 (1H, m), 6.81 (1H, t, J = 8.4 Hz), 7.05–7.35 (8H, m); ^{13}C NMR ($CDCl_3$): δ 19.2, 19.3, 28.1, 41.2, 41.4, 44.4, 44.8, 45.1, 45.4, 54.1, 54.6, 71.5, 71.7, 117.2, 117.5, 126.1, 126.1, 126.4, 126.6, 126.7, 126.8, 126.9, 127.0, 128.5, 128.6, 128.9, 129.0, 129.4, 129.6, 134.5, 134.6, 137.1, 137.3, 137.8, 142.3, 155.4; Found: C, 78.78; H, 7.83; N, 3.79%. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01%.

In a manner similar to **2a**, *trans*- and *cis*-**2b**, **2c** were obtained.

Benzyl *trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*trans*-2b): Colorless oil. IR (neat, cm^{-1}): 3028, 2935, 1694, 1426, 1219, 1126, 915, 753, 731; ^{1}H NMR ($CDCl_3$): δ 2.62–2.74 (2H, m), 3.64 (1H, dd, J = 4.0, 13.5 Hz), 4.11–4.35 (2H, m), 4.62 (1H, d, J = 12.5 Hz), 4.83 (1H, d, J = 12.5 Hz), 4.86–5.25 (2H, m), 5.31–5.36 and 5.50–5.55 (1H, m), 5.72–5.98 (1H, m), 6.84 (1H, d, J = 3.6 Hz), 6.93–7.00 (3H, m), 7.11–7.49 (10H, m); ^{13}C NMR ($CDCl_3$): δ 41.1, 44.4, 44.7, 53.8, 66.8, 67.0, 117.4, 126.4, 126.6, 126.8, 126.8, 127.4, 127.5, 127.8, 128.0, 128.2, 130.0, 134.6, 135.8, 136.3, 136.8, 143.9, 155.5; Found: C, 81.37; H, 6.67; N, 3.51%. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%.

Benzyl *cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*cis*-2b): Colorless oil. IR (neat, cm^{-1}): 3028, 2935, 1699, 1428, 1220, 1125, 914, 736, 700; ^{1}H NMR ($CDCl_3$): δ 2.69 (2H, dd, J = 8.1, 17.3 Hz), 3.17–3.34 (1H, m), 4.09–4.21 (1H, m), 4.35 (dd, J = 5.9, 13.7 Hz) and 4.49 (dd, J = 5.9, 13.7 Hz) (1H), 5.00–5.25 (4H, m), 5.31 (t, J = 6.9 Hz) and 5.45 (t, J = 6.9 Hz) (1H), 5.76–5.99 (1H, m), 6.80 (1H, t, J = 9.1 Hz), 7.05 (1H, t, J = 5.8 Hz), 7.11–7.35 (12H, m); ^{13}C NMR ($CDCl_3$): δ 41.2, 41.4, 44.5, 44.8, 45.0, 45.3, 54.2, 54.5, 67.0, 67.3, 117.3, 117.6, 126.1, 126.2, 126.4, 126.5, 126.6, 126.7, 126.8, 126.9, 127.5, 127.8, 127.9, 128.0, 128.3, 128.5, 128.9, 129.0, 129.4, 129.6, 134.4, 134.5, 136.9, 137.1, 137.3, 137.6, 142.1, 154.9, 155.0; Found: C, 81.32; H, 6.57; N, 3.44%. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%.

Ethyl *trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*trans*-2c): Colorless oil. IR (neat, cm^{-1}): 3024, 2979, 1693, 1427, 1220, 1127, 914, 752, 699; ^{1}H NMR ($CDCl_3$): δ 0.75 (t, J = 6.9 Hz) and 1.19 (br) (3H), 2.63 (2H, t, J = 7.6 Hz), 3.60 (1H, dd, J = 3.3, 12.9 Hz), 3.70 (2H, q, J = 7.8 Hz), 4.04–4.31 (2H, m), 5.02–5.09 (2H, m), 5.31–5.51 (1H, m), 5.81–5.97 (1H, m), 6.91–7.00 (3H, m), 7.11–7.25 (6H, m); ^{13}C NMR ($CDCl_3$): δ 14.1, 41.1, 44.6, 44.7, 53.4, 53.7, 60.9, 117.2, 126.2, 126.6, 126.8, 128.0, 128.1, 128.2, 129.9, 134.8, 135.8, 137.1, 143.9, 155.7; Found: C, 78.49; H, 7.33; N, 4.25%. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36%.

Ethyl *cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*cis*-2c): Colorless solid. mp 81.6–82.4 °C (from hexane); IR (KBr, cm^{-1}): 3027, 2980, 1696, 1441, 1222, 1129, 916, 759, 709; ^{1}H NMR ($CDCl_3$): δ 1.24–1.31 (3H, m), 2.70 (2H, dd, J = 6.8, 11.1 Hz), 3.14–3.31 (1H, m), 4.07–4.23 (3H, m), 4.29 (dd, J = 5.9, 13.5 Hz) and 4.47 (dd, J = 5.9, 13.5 Hz) (1H), 5.05–5.13 (2H, m), 5.29 (t, J = 6.9 Hz) and 5.43 (t, J = 6.9 Hz) (1H), 5.82–6.00 (1H, m), 6.81 (1H, t, J = 8.4 Hz), 7.04–7.09 (1H, m), 7.11–7.36 (7H, m); ^{13}C NMR ($CDCl_3$): δ 14.7, 41.2, 41.4, 44.2, 44.8, 44.9, 45.2, 54.0, 54.3, 61.3, 117.2, 117.4, 126.0, 126.4, 126.5, 126.7, 126.8, 126.8, 128.5, 128.9, 129.0, 129.3, 129.6, 134.4, 134.6, 137.1, 137.2, 137.3, 137.7, 142.2, 155.2; Found: C, 78.35; H, 7.22; N, 4.13%. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36%.

Addition Reaction of Allylmagnesium Bromide to 3,4-Dihydro-4-phenylisoquinoline (1) (Table 2, Entry 1). Under an argon atmosphere, to magnesium turnings (214 mg, 8.8 mmol) in THF (2 mL) was added a small amount of 1,2-dibromoethane as initiator at room temperature. Then, freshly distilled allyl bromide (484 mg, 4.0 mmol) in THF (2 mL) was added to a reaction mixture over 40 min at −5 °C. After 1 h, the clear supernatant solution of allylmagnesium bromide (0.93 mL, 0.93 mmol) was added slowly (10 min) to the stirred solution of 3,4-dihydro-4-phenylisoquinoline (**1**) (77.4 mg, 0.37 mmol) in THF (4 mL) using a syringe at −78 °C under an argon atmosphere. After stirring for 1 h, saturated aqueous NH_4Cl and ethyl acetate were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was separated by preparative thin-layer chromatography (silica-gel, hexane/Et_2O = 1/1 ×3) to give *cis*-**3** (35.2 mg, 38%) and *trans*-**3** (44.3 mg, 48%).

***cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*cis*-3):** Oil. IR (neat, cm^{-1}): 3024, 2927, 1638, 1600, 1492, 1450, 916, 755, 701; ^1H NMR ($CDCl_3$): δ 1.75 (1H, br, NH), 2.63–2.71 (2H, m), 3.20 (1H, dd, $J = 4.9$, 13.1 Hz), 3.30 (1H, dd, $J = 4.9$, 13.1 Hz), 4.07–4.16 (2H, m), 5.09–5.17 (2H, m), 5.80–5.96 (1H, m), 6.93 (1H, d, $J = 7.6$ Hz), 7.08–7.32 (8H, m); ^{13}C NMR ($CDCl_3$): δ 40.5, 44.8, 48.8, 55.2, 117.6, 125.6, 126.0, 126.1, 128.0, 128.7, 130.2, 135.1, 137.3, 139.0, 144.8; Found: C, 86.49; H, 7.63; N, 5.41%. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62%.

***trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*trans*-3):** Oil. IR (neat, cm^{-1}): 3024, 2941, 1638, 1600, 1492, 1451, 915, 747, 701; ^1H NMR ($CDCl_3$): δ 1.88 (1H, br, NH), 2.51–2.78 (2H, m), 3.01 (1H, dd, $J = 8.2$, 12.5 Hz), 3.45 (1H, dd, $J = 5.3$, 12.6 Hz), 4.10 (1H, dd, $J = 5.6$, 7.6 Hz), 4.21 (1H, dd, $J = 3.3$, 8.6 Hz), 5.13–5.23 (2H, m), 5.77–5.93 (1H, m), 6.85 (1H, d, $J =$ 7.6 Hz), 7.04–7.32 (8H, m); ^{13}C NMR ($CDCl_3$): δ 40.6, 46.1, 50.1, 55.3, 117.7, 125.3, 125.9, 126.1, 128.1, 128.7, 129.7, 135.2, 138.3, 138.6, 144.3; Found: C, 86.33; H, 7.59; N, 5.47%. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62%.

***tert*-Butyl *cis*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*cis*-4):** To a solution of *cis*-**3** (190 mg, 0.76 mmol) in 1,4-dioxane (6 mL) and water (3 mL) were added 1 M (= 1 mol dm^{-3}) aqueous NaOH (1 mL) and di-*tert*-butyl dicarbonate (200 mg, 0.92 mmol) at 0 °C, and the reaction mixture was stirred for 1.5 h at that temperature. After removal of 1,4-dioxane under reduced pressure, citric acid (0.5 M in water) was added to the residue until the solution became pH 2. CH_2Cl_2 was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica-gel, hexane/ethyl acetate = 8/1) to give *cis*-**4** (238 mg, 89%). Colorless oil. IR (neat, cm^{-1}): 3063, 2976, 1691, 1462, 1409, 1226, 1154, 926, 753, 708; ^1H NMR ($CDCl_3$): δ 1.47 (s) and 1.49 (s) (9H), 2.66 (2H, t, $J = 8.4$ Hz), 3.06–3.27 (1H, m), 4.08–4.16 (1H, m), 4.23 (dd, $J = 5.9$, 17.2 Hz) and 4.47 (dd, $J = 5.9$, 13.5 Hz) (1H), 5.05–5.13 (2H, m), 5.21–5.26 and 5.39–5.44 (1H, m), 5.87–6.00 (1H, m), 6.81 (1H, t, $J = 8.4$ Hz), 7.00–7.08 (1H, m), 7.12–7.36 (7H, m); ^{13}C NMR ($CDCl_3$): δ 28.5, 41.3, 41.5, 43.7, 45.0, 45.3, 53.5, 54.6, 79.7, 80.0, 117.0, 117.4, 126.0, 126.1, 126.3, 126.5, 126.8, 126.8, 128.5, 128.6, 128.9, 129.0, 129.3, 129.7, 134.8, 134.9, 137.4, 137.6, 138.0, 142.4, 142.5, 154.2; Found: C, 79.04; H, 7.85; N, 3.78%. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01%.

***tert*-Butyl *trans*-1-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (*trans*-4):** By a similar method described for *cis*-**4**, *trans*-**4** was obtained in 77% yield as colorless solid, which was recrystallized from hexane to give the single crystalline for X-ray crystallographic analysis; mp 82.5–83.3 °C (from hexane). IR (KBr, cm^{-1}): 3025, 2975, 2937, 2890, 1672, 1418, 1228, 1163, 1012, 921, 745, 722; ^1H NMR ($CDCl_3$): δ 1.06 (s) and 1.36 (s) (9H), 2.61 (2H, t, $J = 7.8$ Hz), 3.57 (1H, dd, $J = 3.1$, 13.4 Hz), 4.10–4.29 (2H, m), 5.01–5.08 (2H, m), 5.24–5.28 and 5.43–5.47 (1H, m), 5.90 (1H, td, $J = 7.3$, 16.8 Hz), 6.91–7.01 (3H, m), 7.10–7.25 (6H, m); ^{13}C NMR ($CDCl_3$): δ 27.9, 28.3, 41.1, 44.8, 52.9, 78.9, 116.9, 126.1, 126.5, 126.7, 126.9, 128.0, 128.3, 130.0, 135.0, 135.8, 137.5, 144.2, 154.4; Found: C, 78.76; H, 7.80; N, 3.77%. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01%.

Addition Reaction of Allyllithium[6] to 3,4-Dihydro-4-phenylisoquinoline (1) (Table 2, Entry 2). Under an argon atmosphere, to a solution of allyltriphenyltin (1.95 g, 5.0 mmol) in Et_2O (9.9 mL) was added phenyllithium (4.6 mL, 1.14 M in cyclohexane–Et_2O, 5.3 mmol) at room temperature. Stirring was stopped after 30 min, and the clear supernatant solution of allyllithium (2.5 mL, 0.88 mmol) was added slowly (20 min) to a stirred solution of 3,4-dihydro-4-phenylisoquinoline (**1**) (71.1 mg, 0.34 mmol) in THF (6 mL) using a syringe at −78 °C under an argon atmosphere. The reaction mixture was stirred for 1 h at that temperature. Ethyl acetate and saturated aqueous NH_4Cl were added to the reaction mixture. After the same work-up procedure described in the reaction using allylmagnesium bromide, *cis*-**3** (45.0 mg, 53%) and *trans*-**3** (22.4 mg, 26%) were obtained.

Addition Reaction of Triallylborane[7] to 3,4-Dihydro-4-phenylisoquinoline (1) (Table 2, Entry 3). Under an argon atmosphere, to a solution of 3,4-dihydro-4-phenylisoquinoline (**1**) (73.5 mg, 0.35 mmol) in THF (6 mL) was added triallylborane (52.3 mg, 0.39 mmol) at −78 °C. After stirring for 1 h, 3 M aqueous NaOH and ethyl acetate were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. After the same work-up procedure described in the reaction using allylmagnesium bromide, *cis*-**3** (46.6 mg, 53%) and *trans*-**3** (25.5 mg, 29%) were obtained.

Addition Reaction of Allylzinc Bromide[8] to 3,4-Dihydro-4-phenylisoquinoline (1) (Table 2, Entry 4). To a suspension of zinc powder (820 mg, 12.5 mmol) in THF (2 mL) was added chlorotrimethylsilane (48 μL), and the reaction mixture was stirred for 15 min at room temperature under an argon atmosphere. Then, 1,2-dibromoethane (41 μL) was added to the mixture. After stirring for 30 min, freshly distilled allyl bromide (605 mg, 5.0 mmol) in THF (3 mL) was added to the suspension of activated zinc over 40 min at 0 °C. After 1 h, stirring was stopped, and excess zinc powder was allowed to deposit on the bottom of the flask. The clear supernatant solution of allylzinc bromide (0.47 mL, 0.47 mmol) was added slowly (5 min) to the stirred solution of 3,4-dihydro-4-phenylisoquinoline (**1**) (64.5 mg, 0.31 mmol) in THF (3 mL) using a syringe at −78 °C under an argon atmosphere. After stirring for 2 h, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and then, 2 M aqueous NaOH was added until the solution became pH 9. Et_2O was added to the mixture and the organic layer was separated. The aqueous layer was extracted with Et_2O. After the same work-up procedure described in the reaction using allylmagnesium bromide, *cis*-**3** (53.6 mg, 69%) and *trans*-**3** (10.1 mg, 13%) were obtained.

Addition Reaction of Diallylzinc[9] to 3,4-Dihydro-4-phenylisoquinoline (1) (Table 2, Entry 5). Under an argon atmosphere at −5 °C, to a solution of zinc chloride (204 mg, 1.5 mmol) in THF (2 mL) was added allylmagnesium bromide, prepared from allyl bromide (363 mg, 3.0 mmol) and magnesium turnings (160 mg, 6.6 mmol) in THF (3 mL). Stirring was continued for 1 h at −5 °C, and the resulting clear supernatant solution of diallylzinc (2.6 mL, 0.78 mmol) was added slowly (15 min) to the stirred solution of 3,4-dihydro-4-phenylisoquinoline (**1**) (54.1 mg, 0.26 mmol) in THF (3 mL) using a syringe at −78 °C under an argon atmosphere. The reaction mixture was warmed to room temperature after stirring for 2 h, and stirring was continued for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and 2 M aqueous NaOH was added until the solution became pH 9. Then, Et_2O was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with Et_2O. After the same work-up procedure described in the reaction using allylmagnesium bromide, *cis*-**3** (42.6 mg, 65%) and *trans*-**3** (6.9 mg, 11%) were obtained.

***tert*-Butyl *cis*-1-(3-Hydroxypropyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (5).** To a THF solution (5 mL) of *cis*-**4** (176 mg, 0.50 mmol) was added 1.17 M BH_3–THF solution (0.86 mL, 1.01 mmol) under an argon atmosphere at 0 °C, and the reaction mixture was stirred for 7 h at room temperature. Then, 3 M aqueous NaOH (2.3 mL) and 30% H_2O_2 (2.3 mL) were added to the mixture, and the stirring was continued for 2 h. Next, saturated aqueous $Na_2S_2O_3$ and Et_2O were added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by preparative thin-layer chromatography (silica-gel, hexane/Et_2O = 1/3) to give **5** (152 mg, 82%). Colorless oil. IR (neat, cm^{-1}): 3416, 2932, 1692, 1422, 1365, 1165, 1124, 757, 703; ^{1}H NMR ($CDCl_3$): δ 1.48 (9H, s), 1.67–1.80 (2H, m), 1.96–2.04 (2H, m), 2.59 (br) and 2.92 (br) (1H), 3.04–3.24 (1H, m), 3.71–3.76 (2H, m), 4.09–4.45 (2H, m), 5.13–5.19 and 5.31–5.37 (1H, m), 6.79 (1H, t, J = 7.3 Hz), 7.02 (1H, t, J = 6.1 Hz), 7.10–7.33 (7H, m); ^{13}C NMR ($CDCl_3$): δ 28.4, 29.1, 29.6, 33.3, 33.3, 43.5, 44.7, 45.0, 45.2, 53.7, 54.7, 62.1, 62.4, 79.9, 80.0, 125.9, 126.0, 126.2, 126.3, 126.5, 126.7, 126.8, 126.8, 128.4, 128.5, 128.8, 128.9, 129.2, 129.5, 137.1, 137.6, 138.2, 138.3, 142.3, 142.3, 154.4, 154.7.

(6*S,10b*R**)-Hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline (7).** To a solution of **5** (140 mg, 0.38 mmol) in pyridine (3 mL) was added TsCl (145 mg, 0.76 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h. After addition of water and Et_2O, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and trifluoroacetic acid (0.5 mL) in CH_2Cl_2 (2 mL) was added to the residue at 0 °C. The reaction mixture was then stirred for 3 h. After neutralization of the reaction mixture with 1 M aqueous NaOH, CH_2Cl_2 was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica-gel, ethyl acetate/MeOH = 9/1) to give **7** (74.8 mg, 79%).

Oil. IR (neat, cm^{-1}): 3022, 2965, 2783, 2730, 1492, 1451, 1376, 1164, 1117, 915, 738, 701; ^{1}H NMR ($CDCl_3$): δ 1.76–2.00 (3H, m), 2.35 (1H, dd, J = 9.9, 17.5 Hz), 2.64 (1H, dd, J = 8.6, 17.8 Hz), 2.89 (1H, dd, J = 5.1, 11.1 Hz), 2.91–3.00 (1H, m), 3.03 (1H, dd, J = 5.4, 11.1 Hz), 3.56 (1H, t, J = 8.2 Hz), 4.19 (1H, t, J = 5.1 Hz), 6.89 (1H, d, J = 7.6 Hz), 7.03–7.11 (1H, m), 7.14–7.30 (7H, m); ^{13}C NMR ($CDCl_3$): δ 22.4, 30.5, 46.3, 54.3, 56.2, 63.7, 125.6, 125.9, 125.9, 126.1, 128.0, 128.8, 129.2, 137.3, 138.8, 145.9; Found: C, 86.33; H, 7.72; N, 5.37%. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62%.

These values are consistent with those reported in the literature.[12]

Experimental Procedure for X-ray Crystallography of *trans*-4. Suitable single crystal *trans*-**4** was obtained by recrystallization from hexane and was mounted on a glass fiber. Diffraction measurement of *trans*-**4** was made on a Rigaku AFC-7R automated four-circle diffractometer by using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The data collections were carried out at -50 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 55.0°. Cell constants and an orientation matrix for data collection were determined from 25 reflections with 2θ angles in the range of 28.62–29.73°. Three standard reflections were monitored at every 150 measurements. In the reduction of the data, Lorentz and polarization corrections and an empirical absorption correction (Ψ scan) were made.

Table 3. Summary of Crystal Data for Compound *trans*-**4**

Empirical formula	$C_{23}H_{27}NO_2$
Formula weight	349.47
Crystal color, habit	colorless, needle
Crystal size/mm^3	0.62 × 0.22 × 0.10
Crystal system	monoclinic
Space group	$P2_1/n$ (no. 14)
Lattice parameters	
a/Å	16.563(7)
b/Å	6.103(4)
c/Å	19.673(4)
β/°	96.78(3)
V/Å^3	1974(1)
Z	4
D_{calcd}/g cm^{-3}	1.175
F_{000}	752.00
μ(Mo Kα)/cm^{-1}	0.74
Reflections measured	9352
Independent reflections (R_{int})	4905 (0.054)
No. of Reflections (All)	4905
No. variables	343
Reflection/parameter ratio	14.30
Residuals: R; R_W	0.088; 0.096
Residuals: $R1$	0.049
No. of reflections to calc $R1$	2754 ($I > 2.0\sigma(I)$)
Goodness of fit Indicator	1.28
$\delta\rho_{max}$; $\delta\rho_{min}$/e Å^{-3}	0.22; −0.23

Crystallographic data and the results of measurements are summarized in Table 3. The structures were solved by direct methods (SIR 92)[13] and expanded using Fourier techniques.[14] All of the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference Fourier maps and refined isotropically. All calculations were performed on a SGI indy computer using the teXsan crystallographic software package of the Molecular Structure Corporation.[15] Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-658110 for compound *trans*-**4**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information

Spectroscopic data of **2a**, **2b**, **2c**, **3**, **4**, **5**, and **7**. These materials are available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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Dedicated to the late Professor Yoshihiko Ito for his outstanding contribution to synthetic organic chemistry.

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